

Cola beverage and delayed elimination of methotrexate

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AIMS

To report a case of severe delayed methotrexate elimination attributable to consumption of a cola beverage.

METHODS

To investigate unexplained low urinary pH in a lymphoma patient treated with high-dose methotrexate.

RESULTS

Unexpected urinary acidity, despite administration of large amounts of sodium bicarbonate, could be attributed to repeated consumption of a cola beverage. It resulted in a delayed elimination of methotrexate and acute renal failure. Discontinuation of cola drinks, increase in calcium folinate rescue and in sodium bicarbonate allowed satisfactory elimination of methotrexate on day 12 after infusion and recovery from renal impairment without other severe toxicity. No other cause of delay in methotrexate elimination could be identified.

CONCLUSIONS

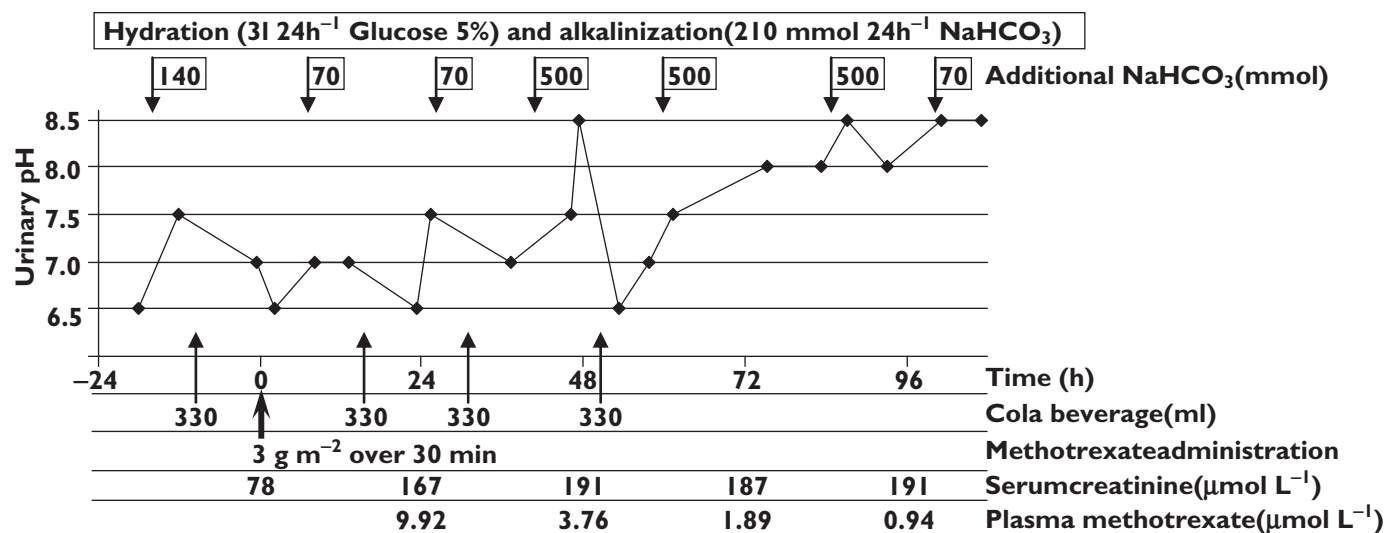
Cola beverages have a low pH due to their phosphoric acid content that is excreted by renal route. We recommend patients receiving high dose methotrexate abstain from any cola drink within 24 h before and during methotrexate administration and until complete elimination of the drug.

Introduction

Methotrexate is an antifolate agent commonly used for the treatment of cancer. It is primarily eliminated by the kidneys [1]. When given at a high dose ($>1 \text{ g m}^{-2}$ intravenously), methotrexate may precipitate in the urine due to limited solubility at pH below 7. Precipitation may lead to renal failure and delayed elimination resulting in toxicity such as severe mucositis, increase in liver enzymes and myelosuppression. Hyperhydration and urine alkalinisation are standard approaches to ensure methotrexate elimination [2]. Close monitoring of urine output and pH and of serum creatinine and plasma methotrexate concentrations is mandatory. We report a case of delayed methotrexate elimination and renal failure associated with a low urinary pH. The unexpected recurrent urinary acidity was related to the consumption of a cola beverage.

Case report

A 56-year-old male (weight 75 kg, body surface area 1.96 m^2) with no prior medical history, was hospitalized for a stage IV diffuse large B-cell non-Hodgkin's lymphoma. Induction chemotherapy was initiated with four cycles of rituximab, doxorubicin, cyclophosphamide, vincristine, bleomycin and prednisolone leading to a complete response. A cycle of high-dose methotrexate (3 g m^{-2}) was then infused over 30 min as prophylaxis of central nervous system involvement. Hyperhydration ($3 \text{ l } 24 \text{ h}^{-1}$ of 5% dextrose solution with electrolyte supplementation) and sodium bicarbonate ($210 \text{ mmol } 24 \text{ h}^{-1}$) were given intravenously as a standard practice. Before starting methotrexate infusion, an initial episode of urinary acidity (pH = 6.5 measured by dipstick test) was corrected with additional infusion of 140 mmol of sodium bicarbonate (Figure 1).

**Figure 1**

Hydration and alkalinization treatment, urinary pH, serum creatinine and plasma methotrexate concentrations over the first 96 h after methotrexate administration

Serum creatinine concentration (78 μmol L⁻¹), creatinine clearance estimated by the Cockcroft & Gault formula (99 ml min⁻¹) and liver function tests were normal before methotrexate administration. The patient had no pleural effusion, ascitis or history of prior renal disease. The patient did not receive any drug known to decrease methotrexate elimination or any nephrotoxic drug. Acute renal failure (serum creatinine: 167 μmol L⁻¹, estimated creatinine clearance: 46 ml min⁻¹) was diagnosed 24 h after methotrexate infusion (Figure 1). Calcium folinate rescue therapy, initially given at 50 mg 6 h⁻¹, was then increased to 200 mg 4 h⁻¹. Impaired renal function resulted in delayed methotrexate elimination with a plasma concentration of 3.76 μmol L⁻¹ at 48 h determined by enzyme-multiplied immunoassay (EMIT®); expected values were 15 μmol L⁻¹ at 24 h, 1.5 μmol L⁻¹ at 48 h and 0.15 μmol L⁻¹ at 72 h).

Recurrent episodes of urinary acidity were observed and the administration of sodium bicarbonate was increased to 500 mmol 24 h⁻¹ in addition to standard alkalinization (Figure 1). Urinary pH was found to lower unexpectedly from 8.5 to 6.5 after the patient returned from the cafeteria having consumed 330 ml of a cola beverage (Coca-Cola®). The patient was asked to stop drinking cola on the third day after methotrexate infusion and the urinary pH was maintained at 8.0 or over. At day 12, serum methotrexate concentration was at 0.1 μmol L⁻¹ and hyperhydration, alkalinization and folinate rescue were stopped. Renal function returned to a normal value 56 days after methotrexate administration (serum creatinine 112 μmol L⁻¹, estimated creatinine clearance: 69 ml min⁻¹). In the meantime, the patient presented a transient grade 2 hypertension, a grade 2 anaemia and a grade 1 fever without any mucositis, skin or liver toxicity. All the adverse

events resolved. No error in methotrexate preparation or administration could be identified.

Discussion

Delayed methotrexate elimination leads to serious toxicity. Delayed elimination may be due to direct nephrotoxicity of methotrexate, insufficient hydration or urine alkalinization, or to drug–drug interactions [1–3]. In our case, the only risk factor we could identify was recurrent urine acidity despite increased sodium bicarbonate administration. Our patient followed a normal diet but used to drink cola beverages during each hospitalization. He did not consume yogurt, buttermilk or cranberry juice, all known to decrease urinary pH [4, 5].

Cola beverages have been identified as a factor lowering urinary pH. De Vries *et al.* have shown the impact of different drinks (water and tea, yogurt, buttermilk, cola beverage and orange juice) on urinary pH in healthy volunteers [4]. Cola beverage (pH = 2.54) and orange juice (pH = 3.64) were the most acidic. Urinary pH was lower in the cola group (pH ≈ 6) than in the orange juice group (pH ≈ 7). This difference can be explained by the various changes occurring during metabolism. The buffer solutions involved in urinary pH regulation are H₂CO₃/HCO₃⁻ (pKa = 6.4), H₂PO₄⁻/HPO₄²⁻ (pKa = 6.8) and NH₄⁺/NH₃ (pKa = 9.2) [4]. Cola beverages contain high doses of CO₂, caffeine, oxalic acid and phosphoric acid (550 mg l⁻¹). Phosphoric acid, an inorganic acid, is not metabolized and its elimination in urine leads to the decrease of urinary pH. Fruit juices and vegetables may be rich in organic acids. However these acids are catabolized and therefore do not lower urinary

pH. Increase in titratable acid in urine starts 2 to 4 h after intake of 1.5 to 2.0 l of cola, is highest 5 to 7 h after intake and lasts for at least 10 h [4]. Jensdottir *et al.* observed that 10 different cola beverages including sugar-free cola had similar low pH (median 2.70, range 2.39–2.88) [6]. A caffeine-free diet cola was also shown to lower substantially urinary pH [7].

In conclusion, due to their acidic properties, we recommend that patients receiving high-dose methotrexate abstain from any cola beverage within 24 h before and during methotrexate administration and until complete elimination of the drug.

Competing interests

There are no competing interests to declare.

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